WHAT MAKES AN IND?

charles river

Introduction

What is an IND?

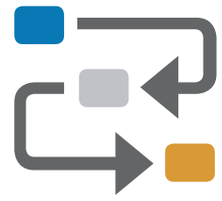
An investigational new drug (IND)* application is a request for Food and Drug Administration (FDA) authorization to administer a drug candidate to humans.

Why is it important?

The FDA reviews the IND application to assure that clinical research subjects will not be subject to unreasonable risk.

IND deadlines

Authorization from the FDA must be received prior to interstate shipment and start of any human clinical trial dosing with a new drug candidate or a new indication for a marketed drug.



The process

The IND requires a complex blend of scientific capabilities and regulatory knowledge to move a candidate – the fruit of a well-designed and executed discovery campaign – to the clinic.

* Clinical Trial Authorization (CTA) applications are IND equivalents for Economic Co-operation and Development (OECD) submissions.

Challenges and Opportunities

Drug development is an intricate and extensive process that requires considerable investment of time, personnel, and resources.

Time

The collection and evaluation of the data for proper characterization of a drug candidate, its properties, and the clinical trial design take careful preparation to ensure maximal efficiency and time management.

Skilled Staff

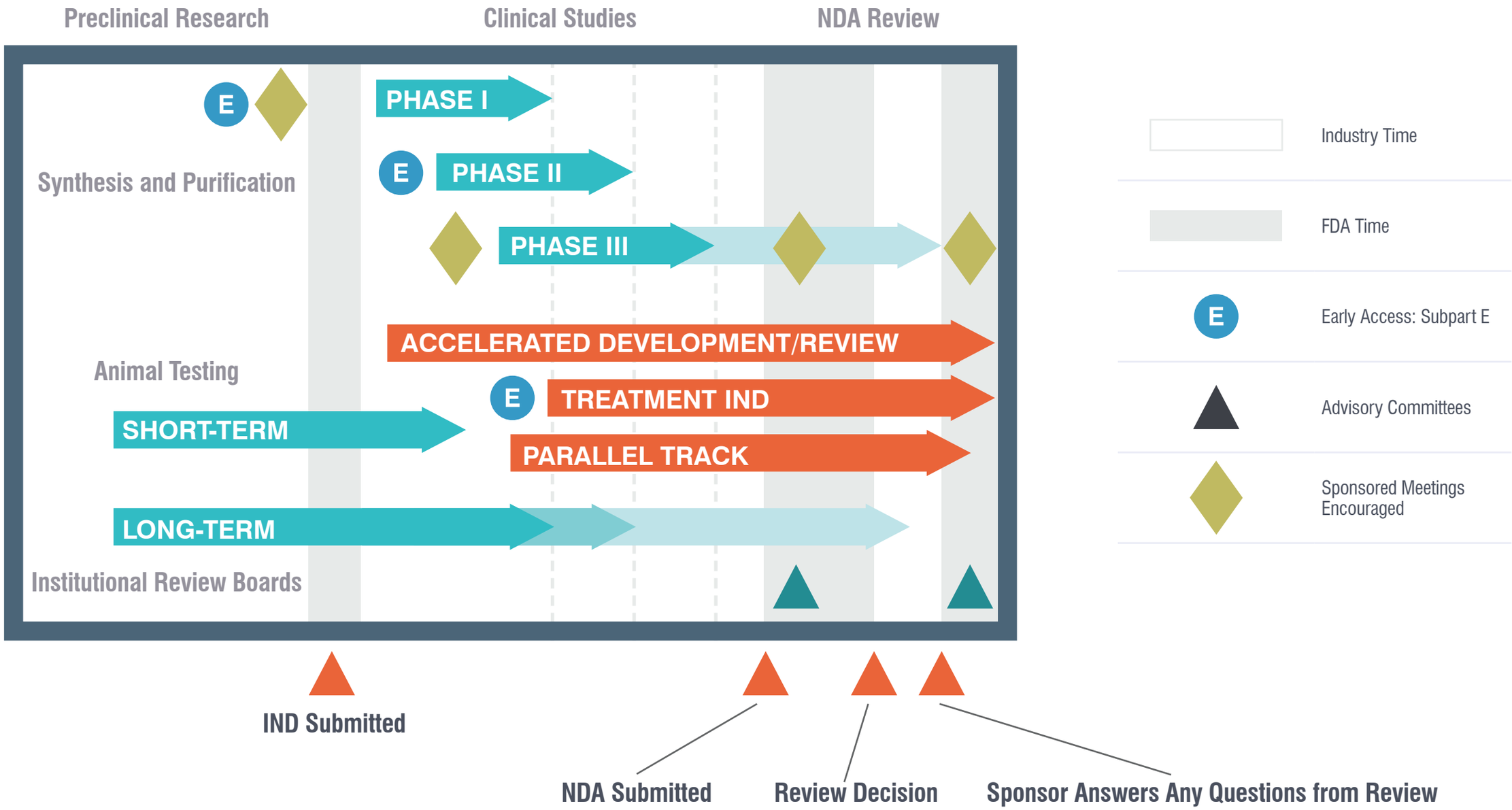
A drug development team is comprised of experts across multiple disciplines and requires a dynamic approach to assure effective use of these talents.

Capital

Each step of the drug development process can incur significant investment.

Thus, careful planning of studies and activities will be critical to minimize cost, maximize the use of time and people, and conserve financial resources, without compromising the quality of data and the success of IND submissions.

A Complex Process



Key Sections of an IND Application

Investigator's Brochure

Comprehensive document summarizing the body of data and information during the discovery, nonclinical development, and clinical development of a drug candidate.

Chemistry, Manufacturing and Control

Information to assure the proper identification, quality, purity, stability, and strength of the drug candidate; method/process of manufacture.

Clinical Trial Protocol

Outline of the clinical trial(s) with details on number of subjects, inclusion criteria, safety exclusions, and description of the treatment plan.

Pharmacology and Toxicology*

Nonclinical section containing pharmacology, PK/PD, ADME, and toxicology (general, safety pharmacology, genetic toxicology) summaries and data.

*In Europe, additional documentation would be required such as an IMPD (Investigational Medicinal Product Dossier).

The Investigator’s Brochure

The investigator’s brochure is a living document maintained by the sponsor. It is the sponsor’s responsibility to update this document regularly in support of their clinical trials.

Clinical Trial Protocols and Designs

This section of an IND outlines investigations in human subjects intended to discover/verify the effects of an investigational drug for its safety and/or efficacy profile.

A comprehensive understanding of the clinical trial design is essential for the planning of a nonclinical program that will support clinical trials:

- Route of administration for nonclinical studies should be the same, or similar, as that intended for clinical studies.
- Early clinical trials should be supported by toxicity studies of at least equivalent duration.
- Depending on the duration of the clinical studies, nonclinical studies may be referred to as subacute, subchronic, or chronic.

Chemistry, Manufacturing and Control Information

This section of an IND outlines the methods used to manufacture the active ingredient of the drug substance and a description of its physical, chemical, or biological characteristics and acceptable limits and analytical methods used to assure the identity, strength, quality, and purity. It also contains information regarding quantitative composition the drug product (active ingredient in formulation).

To support Good Laboratory Practice (GLP)-compliant toxicology studies:

- Characterization of drug substance/drug product is also needed.
- These studies should be conducted with drug substance with an impurity profile reflecting the clinical batch.
- Developing formulations for preclinical safety studies should consider that toxicology studies often employ doses much higher than those used in efficacy studies.

Pharmacology and Toxicology

There are numerous activities within the nonclinical (i.e., all that leads to clinical phases) development program that are needed for the selection and development of a successful drug candidate (IND).

1 **Discovery – Lead selection**

2 **Pharmacology**

3 **Method development and validation**

4 **Toxicology**

5 **Safety pharmacology**

6 **Genetic toxicology**

Failing to account for these critical steps and the resources they require can result in costly delays later in development. Thus, many biotech companies are taking a proactive approach, partnering with CROs for assistance earlier in the process.

Discovery – Lead Selection

The selection criteria of a drug candidate is critical to the success of a drug development program. With 1:10,000 odds of a drug candidate making it to market, you can maximize your chance of success by selecting candidates with ideal properties:

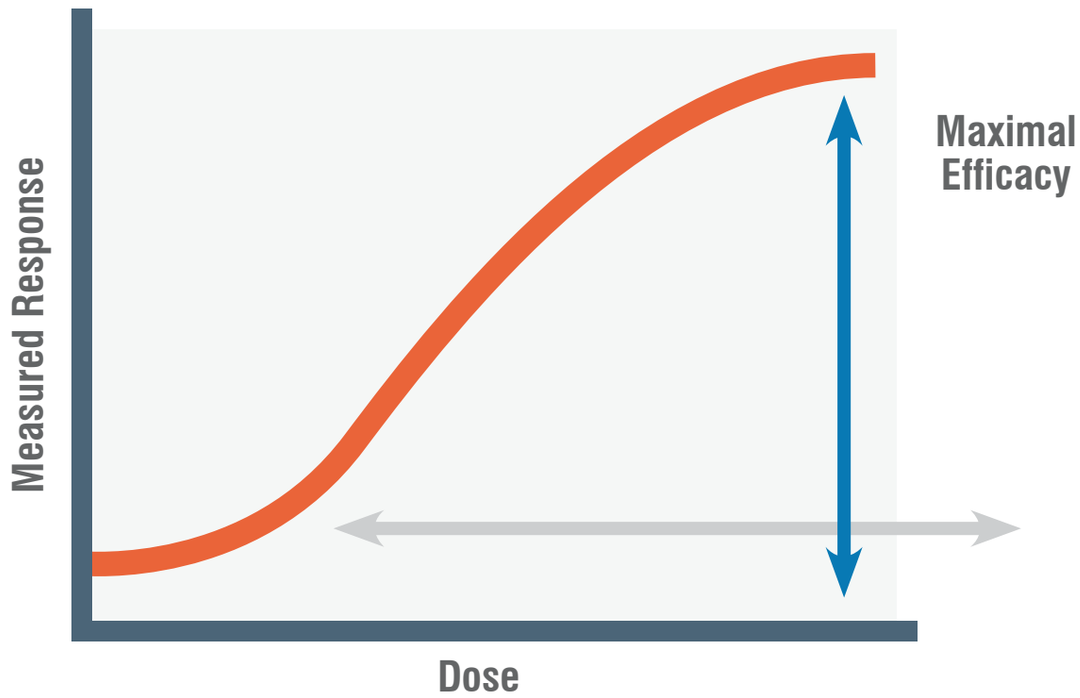
- High potency, efficacy, and selectivity
- Desirable pharmacokinetic profile
- Acceptable therapeutic window (well tolerated)
- Acceptable metabolic profile (may be used for selection of appropriate toxicology animal models)
- Acceptable formulation/composition
- Feasible manufacturing process
- Long-term storage properties and storage conditions
- Patient acceptance of delivery method (i.e., oral, liquid, spray, injection, etc.) and dose regimen

Pharmacology

Efficacy studies are routinely conducted for drug candidate selection/prioritization. *In vitro* assays and *in vivo* animal models help demonstrate activity and efficacy of a drug candidate.

- Establish or confirm target engagement/specificity
- Establish or confirm mechanism of action (MoA)
- Opportunity to establish “potential benefit”

Understanding how pharmacology (target and MoA) impacts the interpretation of nonclinical toxicology studies is integral to the effective presentation of nonclinical data in an IND submission.



Method Development and Validation Requirements

Requirements

Selective, sensitive, and validated analytical methods for the quantitative evaluation of drugs (in formulation and biological matrices), their metabolites (analytes), and biomarkers are critical for the successful conduct of nonclinical and clinical studies.

Fundamental parameters for this validation include the following:

- Accuracy
- Precision
- Selectivity
- Sensitivity
- Reproducibility
- Stability

Types of Assays

The types of assays your drug development program may need include:

- Dose formulation analysis
- Bioanalytical analysis for drug and/or metabolites
- Biomarker analysis
- As-needed specialty endpoints/assays
    - Flow cytometry
    - Immunogenicity assays
    - Immune function assays

Nonclinical Toxicology Study Objectives

The data from IND-enabling studies are needed to:

- Estimate a safe starting dose for clinical trials
- Identify potential biomarkers for monitoring toxicity in clinical studies
- Identify potential target organs for toxicity
- Assess reversibility of toxicities
- Establish margin of safety

Other points for consideration:

- Species selection: relevance to humans, i.e., metabolism, pharmacology, etc.
- Route of administration: mimic clinical use, as feasible/appropriate
- Dose levels: multiples of expected clinical doses
- Formulation: appropriate for route and high(er) concentrations
- Endpoints: standard (clinical signs, body weight, clinical pathology, histopathology, etc.) and drug candidate-specific (biomarkers, flow cytometry, immune response, etc.)

Small Molecules vs. Biologics

The nonclinical safety toxicology program should consider the type of drug candidate under development. The nature (drug class) of the drug candidate will dictate what requirements need to be fulfilled.

	Small Molecule*	Biologic**
Species selection	Metabolism as a primary factor; rodent and nonrodent	Pharmacology as a primary factor; may be only one species
Dose selection	Based on toxicity (maximum tolerated dose)	Based on pharmacology or maximum feasible dose
Safety pharmacology	Stand-alone studies	Part/all may be in toxicology studies
Genetic toxicology	Required (expected)	May not be required
Reproductive toxicology	Required (expected) – two species	One species – weight of evidence
Carcinogenicity	Required (expected) – two species	One species – weight of evidence

***Guideline:**
FDA Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

****Guideline:**
Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)

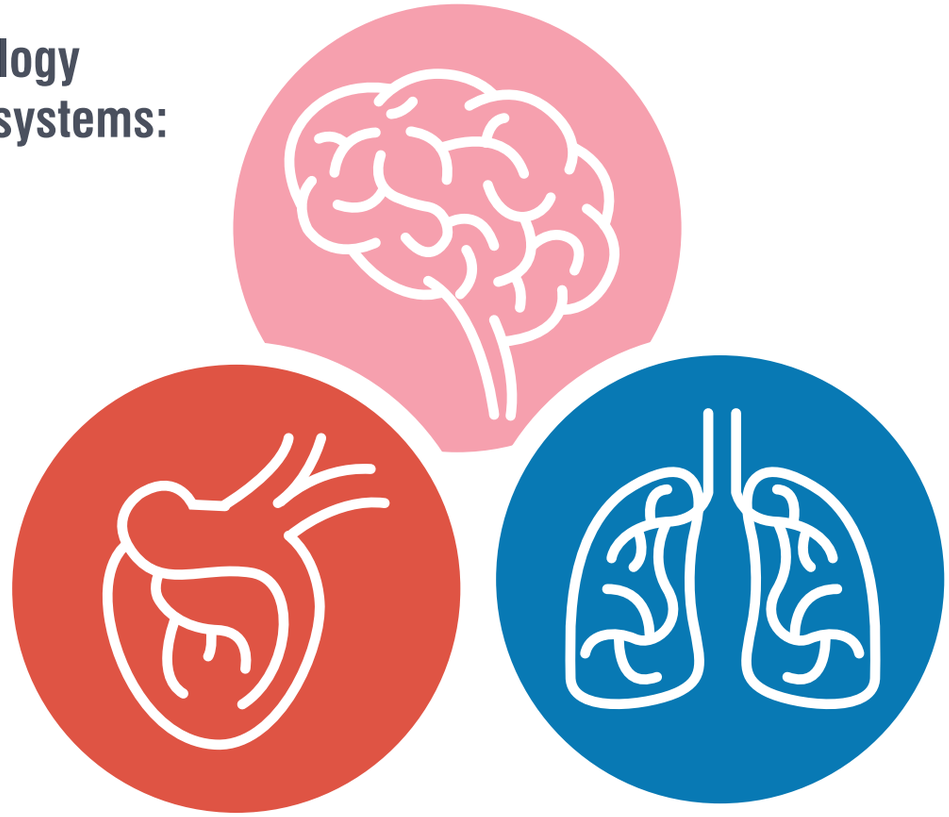
Safety Pharmacology

ICH S7A and S7B guidelines for the conduct of safety pharmacology evaluations recommend a core battery of studies on three vital systems:

- Central nervous system
- Cardiovascular system
- Respiratory system

Additional systems (e.g., renal and gastrointestinal) may be needed.

Because every compound is unique, it takes specialized knowledge of regulatory guidance to develop the most appropriate safety pharmacology program.



S7A guideline:
Safety Pharmacology Studies for Human Pharmaceuticals S7A

S7B guideline:
The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Genetic Toxicology

Depending on the drug candidate and therapeutic indication, genetic toxicology may be required; however, study type, scope, and method of conduct can differ among drug candidates.

Some common assays/tests used to determine a compound's potential genotoxicity are:

- *In silico* analysis (in discovery phase)
- Screening Ames assay (in screening cascade)
- Bacterial mutation Ames assay
- *In vivo* micronucleus study
- Cytogenetic test for chromosomal damage (chromosome aberration, *in vitro* micronucleus, or mouse lymphoma assay)

A clear understanding of the drug candidate is needed to account for regulatory requirements and choice/design of assays.

Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

Other Studies

In support of clinical trials of longer duration, to widen the potential patient pool, and to provide sufficient nonclinical data for market approval via new drug application (NDA), additional studies may need to be completed.

These studies may include:

- Chronic toxicology studies
- Carcinogenicity studies
- Developmental and reproductive toxicity studies
    - Embryo/fetal development (rodent and nonrodent species)
    - Fertility
    - Pre- and postnatal development
    - Juvenile
- Phototoxicity and skin studies (irritation, corrosion, sensitization) (as needed)
- Immunotoxicity studies (as needed)
- Disease models/special populations (as needed)

SEND Requirements

What is SEND?

CDISC SEND is the Clinical Data Interchange Standards Consortium Standard for Exchange of Nonclinical Data, an FDA standard data format/terminology that is required for submission of nonclinical study data to the FDA.

It allows the FDA to:

- Have a standard mechanism for review of data
- Perform comparative and more in-depth analysis of data
- Have harmonized terminology

The benefits to Industry are:

- Standard format and delivery mechanism
- Efficient interactions with both vendors and regulators
- Support of a faster time to market

For more information on SEND, please click here.

Choosing a Partner

Given the tremendous cost and ever-changing landscape of today's drug development, companies large and small are turning to outsourcing for all or part of their programs. Choosing the right partner can greatly accelerate a drug's journey to market while the wrong partner can introduce unnecessary risk and costly delays. Beware of inexperienced or piecemeal providers, whose poor planning and execution can result in the need to repeat or perform additional studies. The extra work balloons your budget, extends your timelines and compromises your ability to make it to market first.

Consider your potential partner's:

- Capacity to perform the work within your timelines
- Continued investment in technology
- Scientific understanding of your molecule
- Ability to move your drug seamlessly through development
- Regulatory knowledge for your intended market
- Reputation and record of success

About Us

Charles River Laboratories is a leading contract research organization with a deep scientific network and world-class facilities around the globe. Leveraging the industry's most comprehensive portfolio of capabilities and decades of combined biotech and pharma experience, our team is uniquely capable of moving your drugs through development.

Every step of the way:

Scientific Advisory Services

Our team of industry-proven professionals is adept at navigating the ever-changing landscape of drug development. Applying a collaborative approach and deep understanding of each molecule, our Scientific Advisors shape the best strategy to advance your novel therapies into and through clinical trials.

Customized Program Design

Drawing from the industry's most comprehensive portfolio, our team can reduce risk and accelerate timelines with programs tailored to your type of drug, anticipated MoA, regulatory strategy and clinical objectives.

Program Conduct and Oversight

Your program conducted at Charles River can be overseen by an experienced Scientific Advisor, and carried out by team of scientists and technical staff dedicated to drug discovery and development.

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Resources

ICH Guidelines

FDA Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Charles River IND-Enabling Studies

Build a customized IND Gantt Chart

Scientific Advisory Services

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